PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P045080PCT DBO/do	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/NL 03/00422	International filing date (day/month/year) 11.06.2003	Priority date (day/month/year) 11.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/565		
Applicant PANTARHEI BIOSCIENCE B.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12.01.2004	05.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Albayrak, T Telephone No. +49 89 2399-7519

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL 03/00422

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-40 as originally filed

Claims, Numbers

1-16 received on 10.06.2004 with letter of 09.06.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL 03/00422

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	-

2. Citations and explanations

see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/NL 03/00422

Re Item I

The basis of this written opinion is the description as originally filed and the claims received on 10.06.2004

Re Item V

Reference is made to the following documents; unless otherwise indicated, reference is made to the relevant passages emphasized in the Search Report.

D1: WO 01/85154 A (UNIV OREGON HEALTH SCIENCES ;OFFNER HALINA (US); GOVERNMENT OF THE) 15 November 2001 (2001-11-15)

D2: DE 199 17 930 A (SCHERING AG) 19 October 2000 (2000-10-19)

D3: HOLINKA C F ET AL: "COMPARISON OF EFFECTS OF ESTETROL AND TAMOXIFEN WITH THOSE OF ESTRIOL AND ESTRADIOL ON THE IMMATURE RAT UTERUS" BIOLOGY OF REPRODUCTION, SOCIETY FOR THE STUDY OF REPRODUCTION, CHAMPAIGN, IL, US, vol. 22, no. 4, 1980, pages 913-926, XP001037210 ISSN: 0006-3363

D4: HOLINKA C F ET AL: "IN VIVO EFFECTS OF ESTETROL ON THE IMMATURE RAT UTERUS" BIOLOGY OF REPRODUCTION, SOCIETY FOR THE STUDY OF REPRODUCTION, CHAMPAIGN, IL, US, vol. 20, no. 2, March 1979 (1979-03), pages 242-246, XP001022978 ISSN: 0006-3363

D5: JANSSON L ET AL: "ESTROGEN INDUCES A POTENT SUPPRESSION OF EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS AND COLLAGEN-INDUCED ARTHRITIS IN MICE" JOURNAL OF NEUROIMMUNOLOGY, ELSEVIER SCIENCE PUBLISHERS BV, XX, vol. 53, no. 2, 1994, pages 203-207, XP001026625 ISSN: 0165-5728

The subject-matter of the present application is the provision of pharmaceutical compositions for the treatment of immune mediated disorders.

1. **Novelty**

For the IPER claim 1 has been interpreted as a second-medical-use-claim (swiss-format) despite the fact that the wording reads "use of an estrogenic component... in the manufacture of a pharmaceutical composition for use in a method of treating...".

For the sake of clarity the words "for use in a method" have been disregarded.

None of the documents cited in the ISA disclose explicitly the compounds of present claim 1 for the claimed treatment. The pharmaceutical compositions of claims 12-16 are not described.

Claims 1-16 are therefore novel over the prior art.

2. **Inventive step**

The problem underlying the present application is the treatment of immune mediated disorders. The solution, according to the applicant, was the administration of estrogenic derivatives of formula 1 of claim 1.

D2, which is regarded as the closest prior art, discloses estrogenic compounds for the treatment of inflammatory diseases and immune mediated disorders. The objective technical problem of the application has therefore to be regarded as to provide alternative compounds for the treatment of immune mediated diseases.

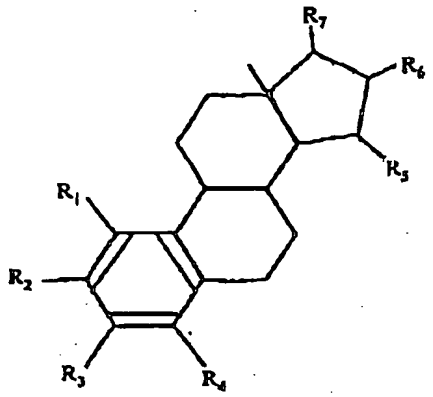
The present compounds of claim 1 fall within the scope of formula 1 of D2. Therefore claim 1 has to be regarded as being a selection of invention on those of D2, which is obvious for those skilled in the art. Such a selection can be regarded as inventive on D2 provided that a surprising or unexpected effect is achieved. However, such appear not to be the case.

Therefore it appears, that the subject-matter of claims 1-16 does not meet the criteria of Art. 33 (3) PCT.

CLAIMS

(57)

1. Use of an estrogenic component selected from the group consisting of: substances represented by the following formula



in which formula R_1, R_2, R_3, R_4 independently are a hydrogen atom, a hydroxyl group or an alkoxy group with 1-5 carbon atoms; each of R_5, R_6, R_7 is a hydroxyl group; no more than 3 of R_1, R_2, R_3, R_4 are hydrogen atoms;

precursors capable of liberating a substance according to the aforementioned formula when used in the present method, which precursors are derivatives of the estrogenic substances wherein the hydrogen atom of at least one of the hydroxyl groups has been substituted by an acyl radical of a hydrocarbon carboxylic, sulfonic acid or sulfamic acid of 1-25 carbon atoms; tetrahydrofuranyl; tetrahydropyranal; or a straight or branched chain glycosydic residue containing 1-20 glycosidic units per residue; and

mixtures of one or more of the aforementioned substances and/or precursors;

in the manufacture of a pharmaceutical composition for use in a method of treating or preventing an immune mediated disorder in a mammal, said immune mediated disorder being selected from the group consisting of autoimmune diseases; rheumatoid arthritis; osteoarthritis; insulin dependent diabetes (type I diabetes); systemic lupus erythrematosis; psoriasis; immune pathologies induced by infectious agents, viral infections or bacterial infections; tuberculosis, lepromatous leprosy; transplant rejection; graft versus host disease; atopic conditions; eosinophilia; conjunctivitis and glomerular nephritis, and said method comprising the administration of a therapeutically effective amount of the estrogenic component to said mammal.

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2. Use according to claim 1, wherein R_3 represents a hydroxyl group or an alkoxy group.

3. Use according to claim 1 or 2, wherein at least 3 of the groups R_1, R_2, R_3 and R_4 represent hydrogen atoms.

4. Use according to any one of claims 1-3, wherein the estrogenic component exhibits an 8β, 9α, 13β, 14α configuration of the steroid-skeleton. ~~the precursors are derivatives of the estrogenic substances wherein the hydrogen atom of at least one of the hydroxyl groups has been substituted by an acyl radical of a hydrocarbon carboxylic, sulfonic acid or sulfamic acid of 1-25 carbon atoms; tetrahydrofuranyl; tetrahydropyranal; or a straight or branched chain glycosydic residue containing 1-20 glycosidic units per residue.~~

5. Use according to any one of claims 1-4 , wherein the method comprises the uninterrupted administration of the estrogenic component during a period of at least 5 days, preferably of at least 30 days.

6. Use according to any one of claims 1-5, wherein the method comprises oral or subcutaneous administration of the estrogenic component.

7. Use according to claim 6, wherein the method comprises oral administration.

8. Use according to any one of claims 1-7, wherein the estrogenic component is administered in an amount of at least 1 μg per kg of bodyweight per day, preferably of at least 5 μg per kg of bodyweight per day.

9. Use according to any one of claims 1-8, wherein the immune mediated disorder is a T-lymphocyte mediated disorder and/or a chronic inflammatory disease.

~~10.Use according to any one of claims 1-9, wherein the immune mediated disorder is selected from the group consisting of autoimmune diseases; rheumatoid arthritis; osteoarthritis; insulin dependent diabetes (type I diabetes); systemic lupus erythrematosis; psoriasis; immune pathologies induced by infectious agents, viral infections or bacterial infections; tuberculosis,~~

~~lepromatous leprosy; transplant rejection; graft versus host disease; atopic conditions; eosinophilia; conjunctivitis and glomerular nephritis.~~.

~~11.~~10. Use according to claim ~~9~~10, wherein the immune mediated disorder is a Th1 mediated disorder.

~~12.~~11. Use according to any one of claims 1-~~10~~1, wherein the immune mediated disorder is selected from the group consisting of multiple sclerosis, rheumatoid arthritis, osteoarthritis, insulin dependent diabetes (type I diabetes), systemic lupus erythrematosis and psoriasis.

~~13.~~12. A pharmaceutical formulation comprising the estrogenic component as defined in claim 1, an immunotherapeutic agent and a pharmaceutically acceptable excipient.

~~14.~~13. The pharmaceutical formulation according to claim 1~~2~~3, wherein the formulation comprises at least 10 µg of the estrogenic component.

~~15.~~14. The pharmaceutical formulation according to claim 1~~2~~3 or 1~~3~~4, wherein the formulation comprises at least 1 µg of the immunotherapeutic agent.

~~16.~~15. The pharmaceutical formulation according to any one of claims 1~~2~~3-1~~4~~5, wherein the immunotherapeutic agent is selected from the group consisting of anti-inflammatory agents; D-penicillamine; 4-aminoquinoline agents; azathioprine; methotrexate; cyclosporin; monoclonal antibodies to T lymphocytes,adhesion molecules ors to cytokines and growth factors; Tumor Necrosis Factor Receptor (TNFR)-IgG; IL-1 receptor antagonists; ICE inhibitors; betaferon; vitamin D; 1α,25-dihydroxyvitamin D_3 and 1α,25-dihydroxyvitamin D_2; agents that specifically bind a molecule selected from the group consisting of a T cell receptor, an antigen and a HLA molecule; organic gold derivatives such a gold sodium thiomalate, aurothioglucose, or auranofin; an angiogenesis inhibitor.

~~17.~~16. An oral unit dosage form comprising a pharmaceutical formulation according to any one of claims 1~~2~~3-1~~5~~6.